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In Reply

We thank Dr. Macbeth for his comments on our article, "Survival Outcomes in Asymptomatic Patients with Normal Conventional Imaging (CI) but Raised Carcinoembryonic Antigen Levels (CEA) in Colorectal Cancer Following Positron Emission Tomography-Computed Tomography Imaging (PET-CT)," which has been recently published in this journal [1]. The points raised emphasize the challenges encountered in interpretation of data from meta-analyses containing heterogeneous results. Indeed, the author himself in the study by Mokhles et al. demonstrated no significant overall survival (OS) advantage in 16 selected randomized clinical trials of primary surveillance for colorectal cancer (CRC) patients [2].

Firstly, we acknowledge the limitations linked to data interpretation in cohort observational studies and preferably the need for a randomized clinical trial in order to provide sufficient evidence to influence clinical practice. However, conducting a randomized clinical trial to validate the approach of secondary surveillance in this unique cohort of high-risk patients is a significant undertaking; the logistical and ethical barriers in a comparative study requiring patients to be randomized to PET-CT versus no PET-CT arms in the presence of raised CEA levels need to be taken into account. Notwithstanding the potential biases of a retrospective study, we report a large cohort of 1,200 consecutive and unselected patients on CRC follow-up in a tertiary referral center that indeed minimizes the selection bias. Moreover, the last patient recruited in our study was in 2010, which allowed at least a 5-year follow up of the recruited cohort, thereby minimizing for the immortal time bias [3].

Another issue raised by the author in his response is that of "metastatic disease being considered as systemic rather than a localized problem." Although we agree that this conventional concept is true for most solid cancers, we respectfully disagree that the same concept is universally true for metastatic CRC patients. There are sufficient data that oligometastatic disease amenable to localized treatment options can be treated with radical intent in selected relapsed CRC patients, and in fact long-term remission can be achieved in up to 40% of such patients [4]. In our cohort, 27 of 49 (55%) patients with PET-CT–detected relapsed disease were eligible for further radical therapy, 19 (70%) of these patients went on to receive radical therapy, and 36.8% were proven to be long-term survivors.

In the current economic environment, we acknowledge the need for appraisal of cost-effectiveness of therapeutic or screening approaches in cancer management. Although a detailed quality-adjusted life-year (QALY) analysis was beyond the scope of this study, it is notable that in this large cohort, very few patients (88/1,200 [7.3%]) underwent a PET-CT scan. We do not suggest that PET-CT is used in unselected patients. The cost of a PET-CT at approximately £800 is twice that of a contrast-enhanced computed tomography (CT; £400) and more expensive than magnetic resonance imaging (MRI; £600). In National Institute for Health and Care Excellence (NICE) guidance on CRC, two studies were included in the cost-efficacy analysis of intensive versus conventional follow-up protocols. Both of these were interpreted as showing intensive follow-up to be cost-effective; Renehan et al. calculated a cost of £3,402 per life-year gained [5], and McAfee et al. calculated an additional cost of £15.4 million to detect an additional 853 resectable recurrences, equating to £18,077 per additional resectable recurrence [6]. Neither of these analyses included trials that included PET-CT within the intensive follow-up arm, and it is therefore difficult to relate the additional expense of PET-CT to these analyses. However, French and American studies have demonstrated PET-CT to be a cost-effective method of staging patients with liver metastases prior to radical surgery, largely by avoiding unnecessary surgery on patients found to have occult metastatic disease [7]. In patients found to have an isolated extrahepatic metastasis on other imaging modalities, PET-CT is recommended by NICE prior to considering radical treatment. In patients with isolated hepatic metastasis on CT, the most cost-effective sequence in which to perform MRI and PET-CT is not clear, and NICE has recommended further research evaluation. Of note, the majority of PET-CT–detected relapses eligible for radical treatment in our series were patients with recurrences confined to the liver or pelvis, amenable to radical treatment usually in the form of surgery. Given that PET-CT provides whole body imaging, whereas MRI does not allow detection of distant relapse such as lung metastases, it would seem more logical and cost-effective to sequence PET-CT as the initial investigation, reserving MRI only for cases in which it is clinically required for further evaluation.

Finally, a simple analysis of cost-efficacy would be to look at the additional cost of performing PET-CT over CT alone on 100 patients with an elevated CEA and normal CI. Extrapolating the results from this series, 63 of these patients would be expected to have relapsed disease, of which 55 would be expected to be detected by PET-CT. Fifty-five percent of these would be eligible for radical treatment of the relapse, translating to 30 patients. Performing a PET-CT on 100 patients would cost an additional £80,000, equating to a cost of £2,666 per patient treated potentially with radical intent on recurrence. This is oversimplified because the majority of patients treated with radical intent at recurrence will require further imaging such as MRI, and this does not take into account the relative treatment costs of both curative and palliative treatment. However, in the context of life-years extended free of disease, this far surpasses the QALY that is associated with NICE approval for end of life care (30 kilo).

In summary, we would like to take this opportunity to once again advise caution when interpreting the results of our study

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and the unnecessary use of PET-CT; however, this investigation should be conducted in carefully selected patients who may achieve long-term disease control, if found to be eligible for localized treatment options.

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Disclosures

The authors indicated no financial relationships.

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